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13. ABSTRACT (Maximum 200 words)
This is a Final Progress Report for "Cleavage of Phosphates, Phosphonates, Phosphonothioates, and Phosphonodiesters." It reviews 13 publications on these topics which have been underwritten by this grant.

14. SUBJECT TERMS
Phosphorolysis, micelles, metal cations, iodoso compounds, kinetics, stereochemistry, cyclodextrins

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Enclosure 1

1. Foreword

This is a Final Progress Report for "Cleavage of Phosphates, Phosphonates, Phosphonothioates, and Phosphodiesters," DAAD19-99-1-0286, 1 July 1999 - 30 June 2003. The report reviews 13 publications which have thus far appeared and which acknowledge ARO support from this grant/contract. It is expected that 2 or 3 more publications will appear in the near future.

2. Table of Contents

(not required)

3. List of Appendixes, Illustrations, and Tables

(not applicable)

4. Statement of the Problem Studied

Our principal scientific objective is the development of efficient catalysts for the destruction of organophosphorus toxins and their degradation products. The classes of target compounds are phosphates, phosphonates, phosphonothioates, and phosphodiesters. Focal areas include iodosobenzoate and iodosonaphthoate micellar and polymeric catalysts for the cleavage of phosphates, phosphonates and phosphonothioates, as well as metal cations and metal cation complexes for the cleavage of phosphodiesters and phosphonate monoesters.

5. Summary of the Most Important Results

Note: in this summary, the numbering refers to the listing of publications in 6(a).

1. Dimethyl phosphate and methyl methylphosphonate are cleaved by Ce(IV)-mediated hydrolysis with 91.5% and 88% P-O scission, respectively, and rate accelerations of $\geq 10^{10}$ relative to pH 7 hydrolysis. The hydrolysis of dimethyl phosphate is illustrated by eq. (1), Plate1.

2. Lanthanide-mediated hydrolyses of micellar β-hydroxyhexadecyl *p*-nitrophenyl phosphate (**1**, Plate 1) and hexadecyl *p*-nitrophenyl phosphate (**2**), as well as non-micellar analogues, were accelerated by the tripositive cations of La, Eu, Tb, Er, Tm, and Yb at pH 7, 37 °C. Micellar advantages of 4-13 were observed at 2 mM Ln^{3+}, due to enhanced binding of the cations to the anionic micellar substrates. Tm^{3+} was the most reactive cation, eliciting 10^5-fold hydrolytic rate accelerations.

3. 4-Nitro-1,8-naphthyl phosphate (**3**, Plate 1) is 2-3 orders of magnitude more reactive to basic and metal cation-mediated hydrolysis by Eu^{3+}, Zr^{4+}, or Th^{4+} than its acyclic analogue **4**.

4. Basic cleavages of *p*-nitrophenyl diphenyl phosphate (**5**), *p*-nitrophenyl 1,8-naphthyl phosphate (**6**), and *p*-nitrophenyl biphenyl phosphate (**7**) [see Plate 1] were mediated by α, β, and γ-cyclodextrins. Derived kinetic parameters revealed substantial selectivity for the β-CD/**6** system, with efficient CD-catalyzed cleavage characterized by a high value of k_{cat}/K_{diss}.

5. *o*-Iodosobenzoate (**8**, IBA) and 2,3-iodosonaphthoate (**9**, INA) in aqueous cetyltrimethylammonium chloride (CTACl) micelles, as well as copper metallomicelles **10** [see Plate 1], all at pH 8, cleave phosphonothioates (**13** and **14**, Plate 2), the thiophosphate parathion (**12**, Plate 2), phosphonate **15**, and phosphate **11** (paraoxon, Plate 2). The factors for the kinetic advantages in the cleavages of **14** and parathion (**12**) range from $10^3 - 10^4$. Excess IBA/CTACl

destroys paraoxon and parathion with half-lives of 3.0 and 7.7 min, respectively, at pH 8.0 and 25 °C. Cleavages of **14** and parathion occur by hydrolysis followed by oxidation of the sulfur-containing fragment.

6. Hydrolyses in D_2O (pD 1.7-3.1) of dimethyl phosphonoformate (DMPF, **16**, Plate 2) are accelerated ~1000-4000 times by Zr(IV), Hf(IV), Th(IV), or Ce(IV) cations. Chemoselective cleavages of DMPF are observed, whereby Zr(IV) and Hf(IV) principally direct P-OMe hydrolysis, whereas Th(IV) and Ce(IV) mainly direct C-OMe hydrolysis.

7. Micellar cetyltrimethylammonium iodosobenzoate ((CTA)IBA, **17**, Plate 2) is highly reactive toward paraoxon (**11**) and parathion (**12**). In aqueous solution at pH 9, excess (CTA)IBA mediates their hydrolyses with k_{obs}(max) = 0.014 and 0.0030 s^{-1}, respectively, corresponding to half-lives of 50 sec and 3.8 min. (CTA)IBA merits serious consideration for the remediation of paraoxon or parathion contamination.

8. Micellar (CTA)IBA (**17**) cleaves the P-O ester linkages of bis(*p*-nitrophenyl) phosphate (**18**), methoxycarbonyl phenyl phosphonate (**19**), and hexyloxycarbonyl phenyl phosphonate (**20**) [see Plate 2]. Kinetic advantages of several orders of magnitude are obtained relative to the unassisted hydrolyses.

9. A comprehensive review was written of phosphorolytic reactivity of IBA (**8**, Plate 1) and related nucleophiles. The review appears in *Chemical Reviews*, **102**, 2497-2521 (2002). It contains 148 references.

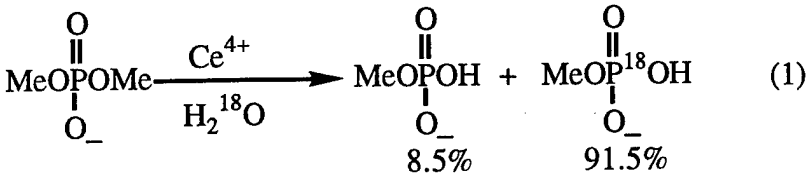
10. The copper metallomicellar hydrolysis of *O*-methyl *O*-4-nitrophenyl phenylphosphonothioate to *O*-methyl phenylphosphonothioic acid takes place with effectively complete inversion of phosphorus; see eq. 2 (Plate 2). This is consistent with a $S_N2(P)$ mechanism.

11. *o*-Iodosobenzoate (**8**) and 2,3-iodosonaphthoate (**9**) cleave NNP (**3**) [see Plate 1] in cationic micelles at pH 9 with rate accelerations of 1200 or 5800, respectively.

12. Eu^{3+} and La^{3+}, and their bis-tris propane complexes, mediate the hydrolysis of dimethyl phosphonoformate (**16**, Plate 2) with C-OMe regiospecificity and substantial rate enhancement. Possible intermediates and metastable constructs for the hydrolytic reaction of **16** and La^{3+} were evaluated by ab initio calculations.

13. Cu-mediated cleavage, coupled with diastereoselective binding and orientational preferences supplied by γ-cyclodextrin, led to substantial kinetic diastereoselectivity in the phosphorolysis of phosphonamiodthiodate diastereomers (S_PS_C)-**21** and (R_PS_C)-**21**; see Plate 2.

PLATE 1



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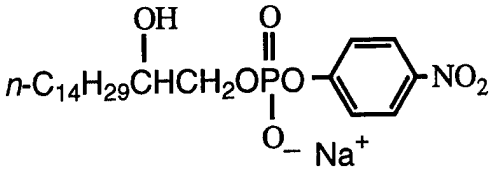
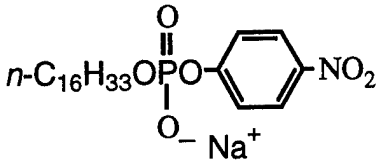


1 (HHNP)



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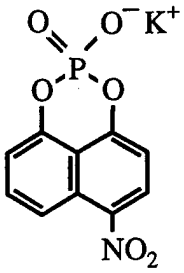

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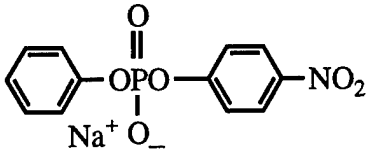
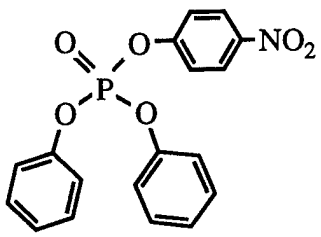


4 (MNPP)



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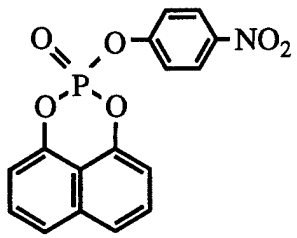

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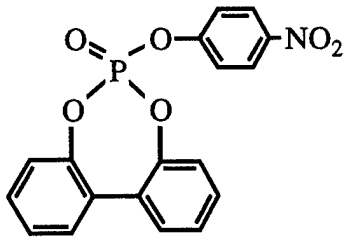

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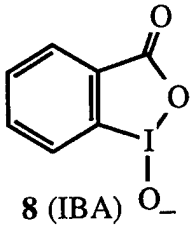

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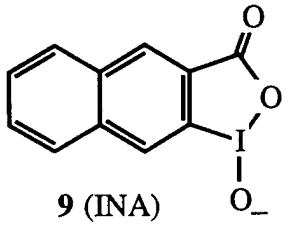

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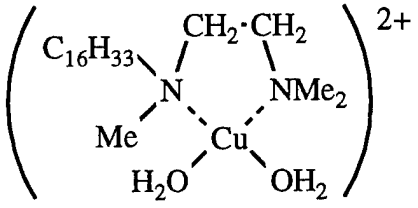

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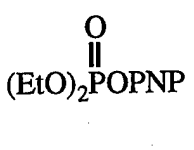
PLATE 2



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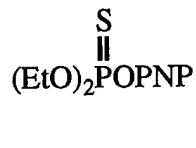

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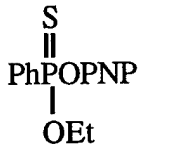

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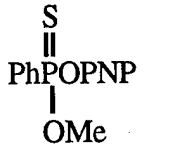

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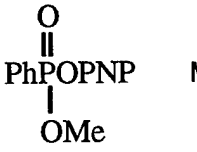

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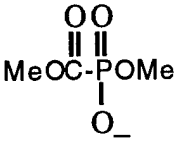

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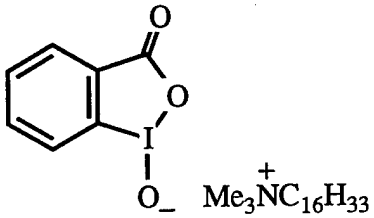
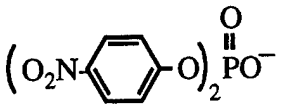


17 (CTA)IBA



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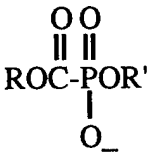
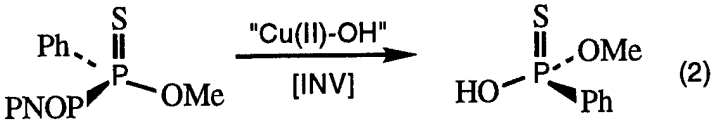
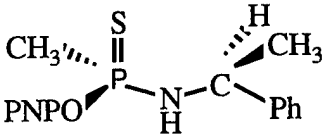
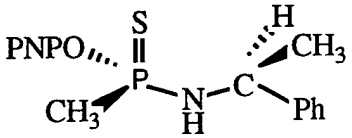


19, R=Me, R'=Ph
20, R=*n*-Hex, R'=Ph





(S_PS_C)-**21**



(R_PS_C)-**21**

6. Publications and Reports

a. Papers published in peer-reviewed journals

1. "Loci of Ceric Cation Mediated Hydrolyses of Dimethyl Phosphate and Methyl Methylphosphonate," R.A. Moss and H. Morales-Rojas, *Organic Lett.*, **1**, 1971 (1999).

2. "Lanthanide Mediated Cleavages of Micellar Phosphodiesters," R.A. Moss and W. Jiang, *Langmuir*, **16**, 49 (2000).

3. "An Unusually Reactive Phosphodiester," R.A. Moss and K.G. Ragunathan, *Tetrahedron Lett.*, **41**, 3275 (2000).

4. "Cyclodextrin-Mediated Hydrolyses of Novel Phosphotriesters," R.A. Moss and P.K. Gong, *Langmuir*, **16**, 8551 (2000).

5. "Kinetics of Cleavage of Thiophosphates and Phosphonothioates by Micellar Iodosobenzoate and Copper Metallomicelles," R.A. Moss and H. Morales-Rojas, *Langmuir*, **16**, 6485 (2000).

6. "Chemoselectivity in Metal Cation Mediated Hydrolyses of a Phosphonoformate Diester," R.A. Moss and H. Morales-Rojas, *J. Am. Chem. Soc.* **123**, 7457 (2001).

7. "Kinetics of Cleavage of Paraoxon and Parathion by Cetyltrimethylammonium Iodosobenzoate," R.A. Moss, S. Kanamathareddy, and S. Vijayaraghavan, *Langmuir*, **17**, 6108 (2001).

8. "Phosphorolytic Cleavages of Phosphate and Phosphonoformate Diesters by Cetyltrimethylammonium Iodosobenzoate," R.A. Moss, S. Vijayaraghavan, and S. Kanamathareddy, Langmuir, **18**, 2468 (2002).

9. "Phosphorolytic Reactivity of o-Iodosylcarboxylates and Related Nucleophiles," H. Morales-Rojas and R.A. Moss, *Chem. Rev.*, **102**, 2497 (2002).

10. "Stereochemical Study of Phosphonothioate Cleavage by a Metallomicelle," R.A. Moss, P.K. Gong, and H. Morales-Rojas, *Organic Lett.*, **4**, 1835 (2002).

11. "Comparative Nucleophilic Reactivities in Phosphodiester Cleavage," R.A. Moss and B.A. McKernan, *Tetrahedron Lett.*, **43**, 4179 (2002).

12. "Phosphonoformate Diester Hydrolysis Mediated by Lanthanide Cations," R.A. Moss and B.A. McKernan, *Tetrahedron Lett.*, **43**, 5925 (2002).

13. "Amplification of Diastereoselectivity by Cyclodextrins in the Copper-Mediated Cleavages of Methylphosphamidothioates," R.A. Moss and J. Tian, *Tetrahedron Lett.*, **44**, 4295 (2003).

b. Papers published in non-peer-reviewed journals or in conference proceedings.

None

c. Papers presented at meetings, but not published in conference proceedings

"Micellar Iodoso- and Iodoxybenzoate Cleavages of Model Phosphonothioates, Thiophosphates, and Related Substrates," R.A. Moss, New Concepts in Decontamination Workshop, Jackson Hole, Wyoming, September 28, 2000.

d. Manuscripts submitted, but not (yet) published.

"Proton exchange and chemoselectivity in metal cation and hydroxide ion hydrolyses of phosphonoacetate diesters," R.A. Moss and P.K. Gong, submitted for publication.

c. Technical reports submitted to ARO

None

7. List of all participating scientific personnel.

Prof. Robert A. Moss, P.I.

Dr. Suseela Kanamathareddy (Postdoctoral)
Dr. Barbara McKernan (Postdoctoral)
Dr. Jingzhi Tian (Postdoctoral)
(Dr.) Hugo Morales-Rojas (Graduate Assistant)*
(Dr.) Saketh Vijayaraghavan (Graduate Assistant)**

*Ph.D. awarded, 2001.
**Ph.D. awarded, 2002.

8. Inventions

None

9. Bibliography

See publications listed under 6(a).

10. Appendixes

None